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CORRESPONDENCE

Using facial analysis technology in a typical genetic clinic: experience from 30 individuals from a single institution

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To the Editor:

We read with interest the article by Mishima et al. [1] about using facial recognition technology on 74 individuals (40 with confirmatory test, 34 with only clinical diagnosis) of Japanese ancestry with diverse congenital dysmorphic syndromes. After omitting those syndromes without a baseline composite image for comparison by the facial recognition technology, their top ten sensitivity rate was 85.7% (42/49). As a follow-up study, we aim to provide further data on the utility of facial analysis technology in the clinical setting. We present data from 30 individuals with craniofacial dysmorphism evaluated at a single institution who underwent additional genetic testing.

All individuals were evaluated by a single geneticist (YAZ) from April 2018 to March 2019. After obtaining approval from the Institutional Review Board of the University of Arkansas for Medical Sciences, a retrospective review identified individuals that: (1) Had no prior known underlying genetic diagnosis and (2) Underwent further genetic testing. Knowing that most clinical geneticists are comfortable making the clinical diagnosis of Down syndrome and that the utility of facial analysis software in this particular condition has already been well documented [2], individuals suspected to have Down syndrome were excluded. The CLINIC application of the Face2Gene web interface (https://www.face2gene.com/) was used. Signed consent was obtained for the image publication. Because the only ubiquitous requirement for enrollment in this study was the subjective presence of facial dysmorphism and given the variability and rather nonspecific nature of concurrent phenotypes (i.e., most had developmental delay and many had growth retardation, but the majority lacked unique distinctive features), only facial photographs were used for analysis without other phenotypic features for analysis. For each suggested syndrome, the "gestalt level" suggested by Face2Gene was recorded as "high," "medium," or "low." We evaluated the performance of Face2Gene (V.19.1.3) by comparing the list of syndromes suggested to the final diagnosis after genetic testing was completed. Lastly, when a final diagnosis was not in the list of the top 30 syndromes suggested by Face2Gene, we determined whether the tool had a preexisting gestalt image available for comparison.

Frontal facial photographs of 30 individuals suspected to have an underlying genetic syndrome with craniofacial dysmorphism were available for review (20 males, average age 5.0 years) (Supplementary Table 1). In addition to the dysmorphic features, common phenotypic traits included developmental delay/intellectual disability (90%), growth retardation (47%), and multiple congenital anomalies (43%). Twelve individuals (40%) had no prior genetic testing performed while 53% previously had chromosomal microarray with a result that was nondiagnostic or incompletely accounting for the phenotype.

Twenty three different conditions were suggested as the #1 match but the gestalt similarity level was "medium" or "high" in only 30% (Supplementary Table 1). At least one final confirmed diagnosis was achieved in 25 individuals (Fig. 1). The tool correctly suggested the diagnosis in the list of possibilities for 11 individuals based exclusively on facial analysis (44%): 7/11 as the top 1 match, 3/11 in the top 10, and 1/11 in the top 20 (Fig. 1). Of note, for these 11 syndromic conditions suggested by Face2Gene, a validated facial model was available in the dataset. When

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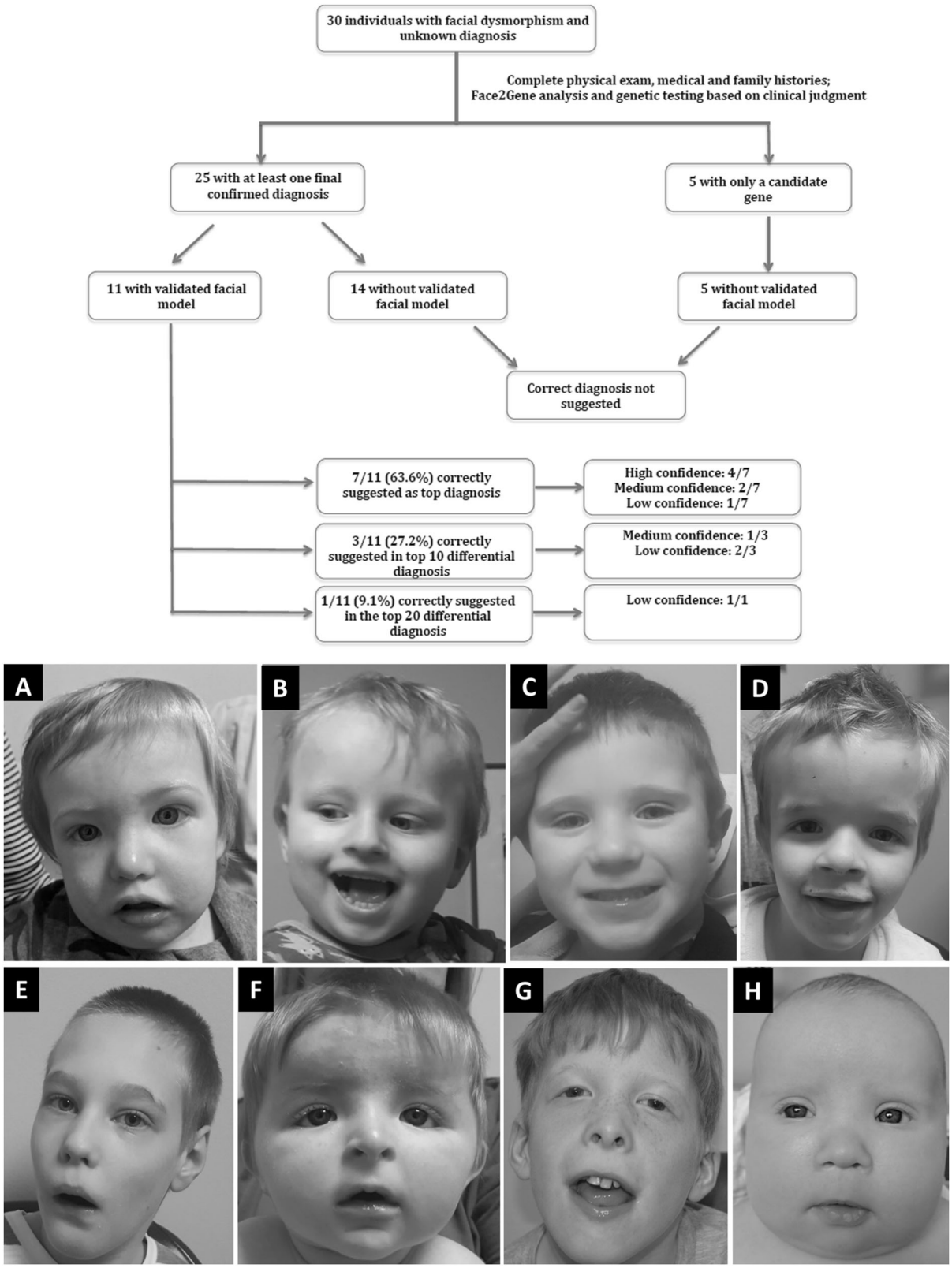

validated facial models of the final diagnosis were available, the top 1, top 10, and top 20 sensitivity rates were 63.6% (7/11), 90.1% (10/11), and 100% (11/11), respectively.

The Face2Gene software developed by FDNA Inc. (Boston, MA, USA) recognizes two-dimensional facial images to detect facial landmarks and uses a deep

◀ **Fig. 1** Top. Diagnostic flow of 30 individuals with facial dysmorphism evaluated using Face2Gene. Bottom. Face2Gene correctly suggested the final diagnosis for several individuals: **a** 5p deletion syndrome for individual F2G-003, **b** Angelman syndrome for individual F2G-004, **c** Interstitial 1p36 deletion for individual F2G-007, **d** Coffin Lowry syndrome for individual F2G-009, **e** Phelan McDermid syndrome for individual F2G-018, **f** Rubinstein Taybi syndrome for individual F2G-028, **g** ATRX syndrome for individual F2G-029, and **h** Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) for individual F2G-035

convolutional neural network learning approach to build de-identified mathematical facial descriptors ("gestalt") [3]. The patient's facial descriptor is compared with over 300 different validated facial syndrome models to quantify similarity (gestalt scores) and to generate a ranked list of matching syndromes. Over the last few years, this tool's utility with high sensitivity and accuracy was shown in a variety of studies [2, 4–10].

Despite mounting evidence of the usefulness of computer assisted syndrome recognition in the research setting, studies exploring its utility in the day-to-day clinical setting are lacking. As in the study by Mishima et al. we provide cases to further document this tool's utility in correctly suggesting relatively common recognizable conditions, such as Angelman, Coffin Lowry, Rubinstein Taybi, and Williams syndrome. We add other conditions to this list including BPES, ATRX, lateral meningocele syndrome, Malan syndrome, Phelan McDermid syndrome, and atypical 1p36 deletion syndrome (the 1p36 deletion in this individual does include *SKI* and other genes in the postulated distal critical region responsible for the common craniofacial features seen in this syndrome) [11]. The combined data from Mishima et al. and this study show a top ten sensitivity rate of 86.6% (52/60) in the routine clinical setting for conditions with validated facial model, exclusively based on facial analysis. Of note, the day-to-day sensitivity of this tool in clinical practice is likely to be lower given the currently limited dataset of validated facial syndromes available for comparison. As the Face2Gene application expands its validated models to include additional syndromic conditions, its clinical application will further improve. Adding phenotypic features using standardized terminology already allows for comprehensive matching, not limited to conditions with a validated facial model. While this approach improves the ranking for suggested matches in relation to the final diagnosis [12], it was outside of the scope of the current project.

Compliance with ethical standards

Conflict of interest KWG is a consultant to FDNA, the company offering the Face2Gene application.

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